Figure 1

The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

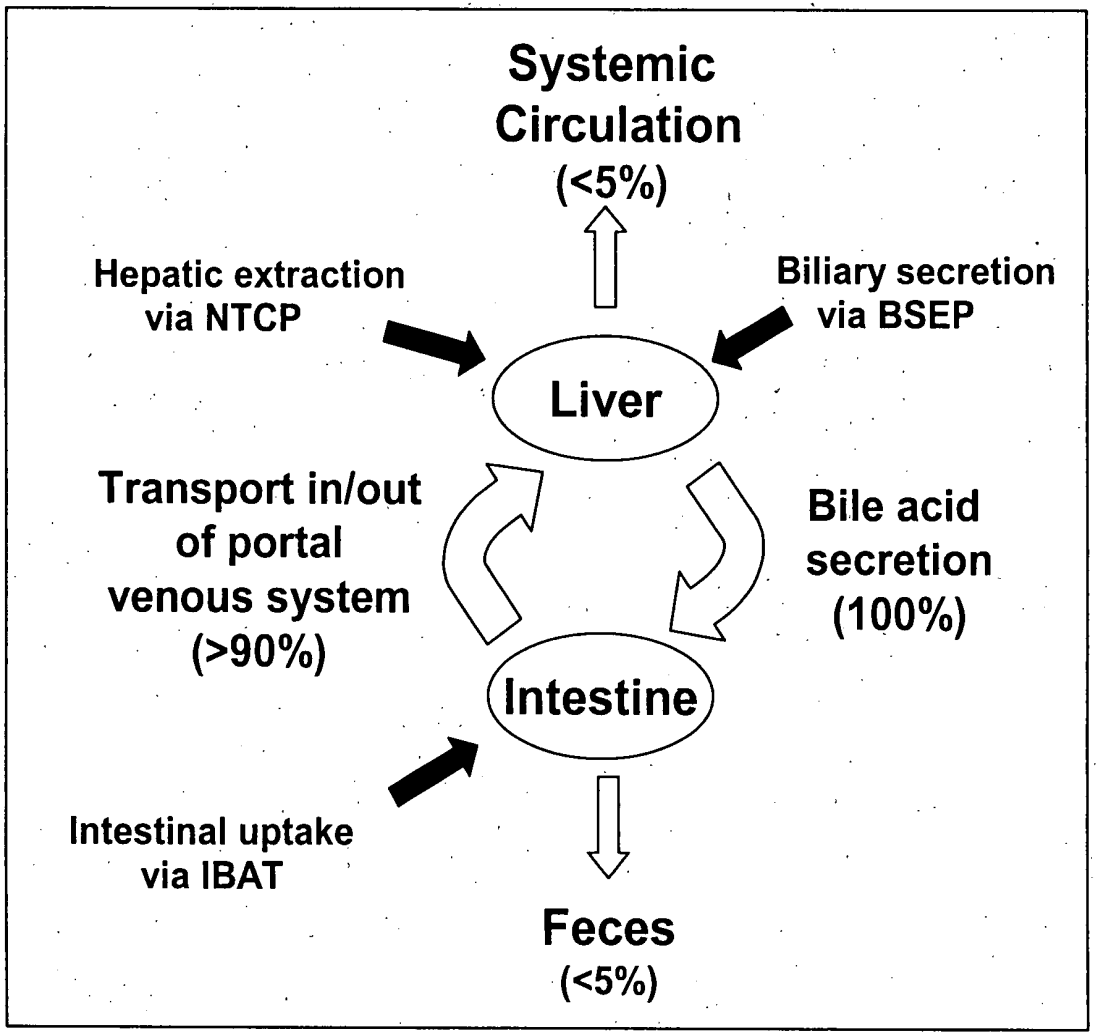
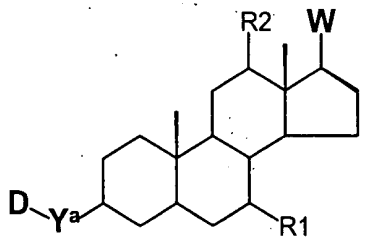
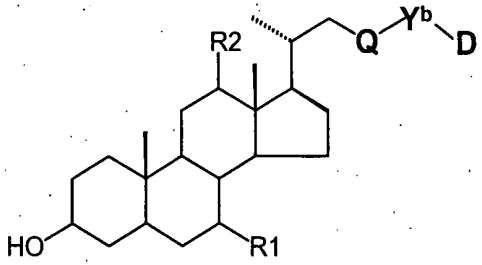


Figure 2

Bile Acid Prodrug Derivatives for Sustained Release of Drugs



(I-a)

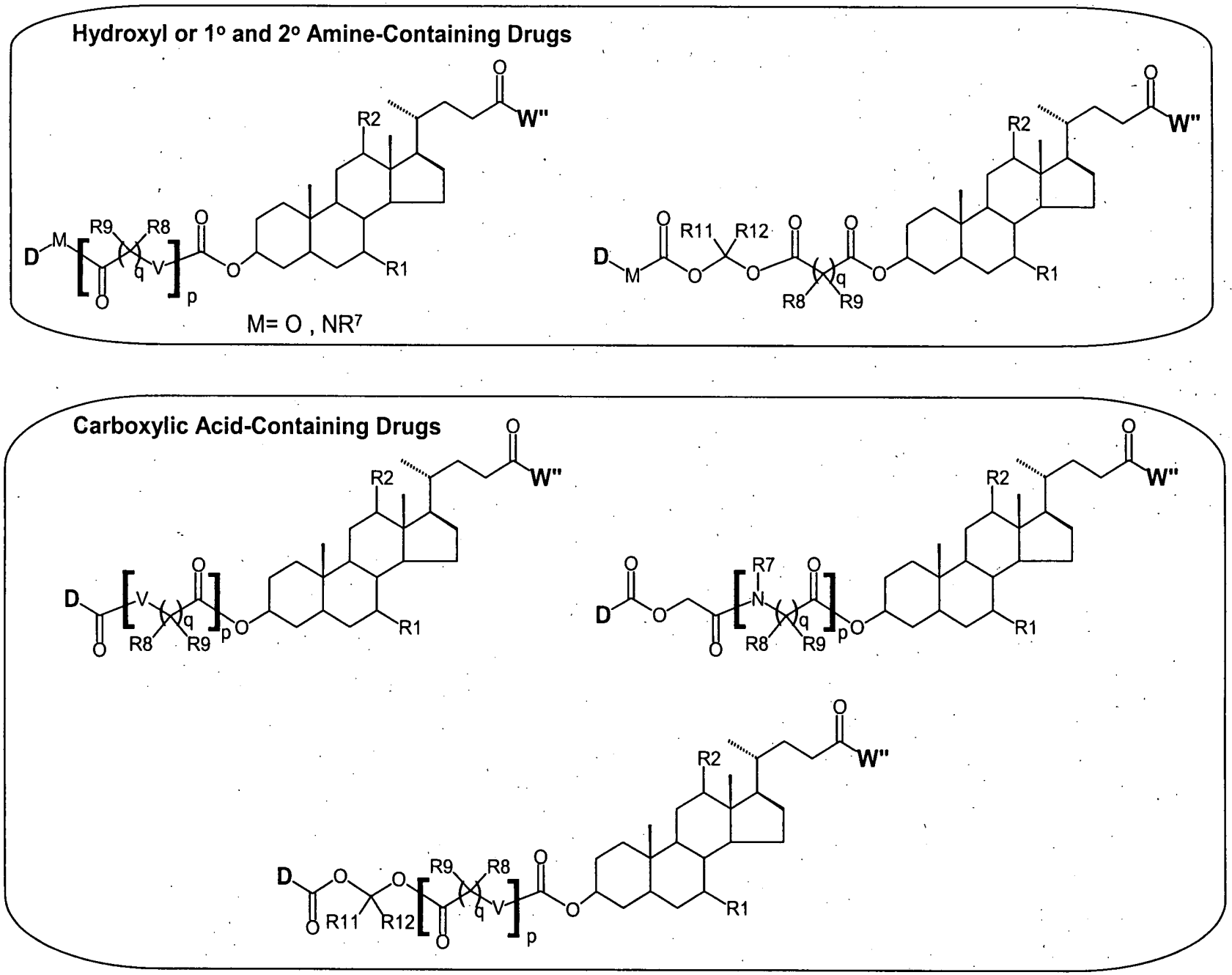


(I-b)

Y^a, Y^b are cleavable linker groups
D is a drug moiety
Q is CH_2 or O
W is selected from the group consisting of -$CH(CH_3)$W' where W' is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of -COOH, -SO_3H, -SO_2H, -$P(O)(OR^6)(OH)$, -$OP(O)(OR^6)(OH)$, -OSO_3H and pharmaceutically acceptable salts thereof

R1 = R2 = α-OH (from Cholate)
R1 = α-OH, R2 = H (from Chenodeoxycholate)
R1 = β-OH, R2 = H (from Ursodeoxycholate)
R1 = H, R2 = α-OH (from Deoxycholate)
R1 = β-OH, R2 = α-OH (from Ursocholate)
R1 = R2 = H (from Lithocholate)

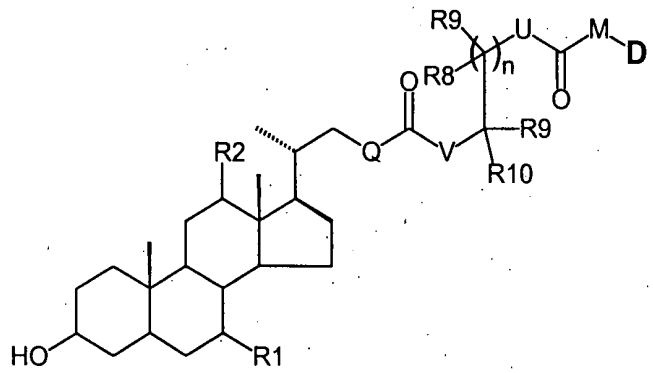
Figure 3- Generic Structures of Preferred Bile Acid C-3 Derivatives

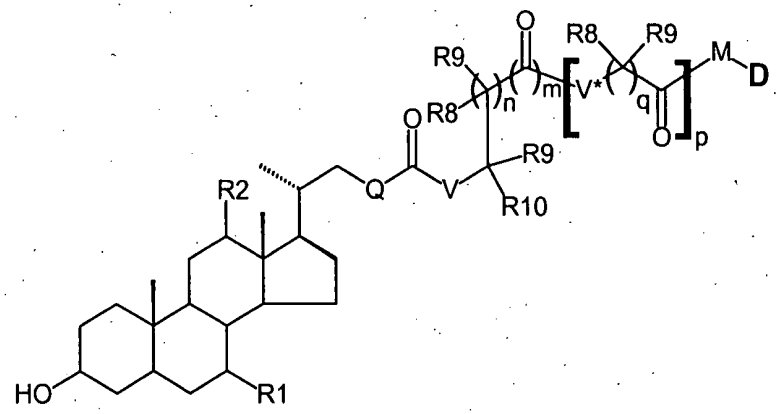


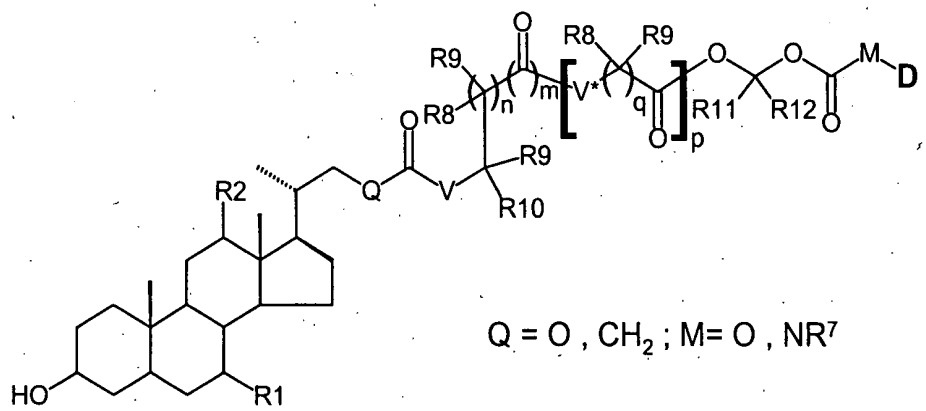
W" is OH , $NHCH_2CO_2H$, $NHCH_2CH_2SO_3H$ or pharmaceutically acceptable salts thereof

Figure 4- Generic Structures of Preferred Bile Acid C-24 Derivatives

Hydroxyl or 1° and 2° Amine-Containing Drugs

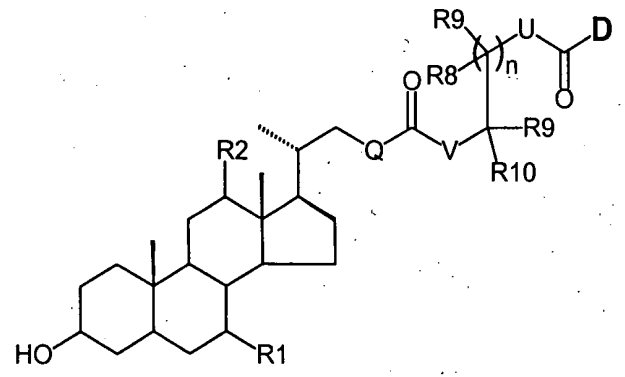






Q = O , CH_2 ; M= O , NR^7

Carboxylic Acid-Containing Drugs



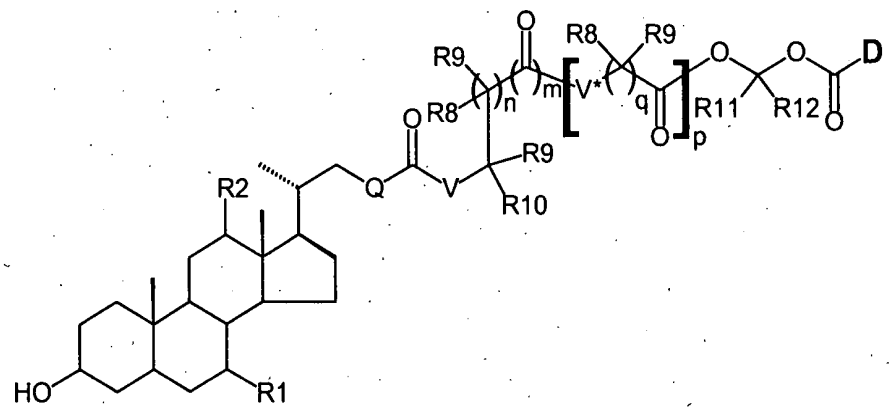
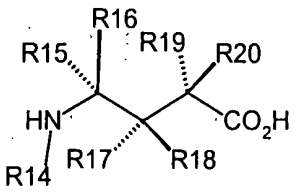
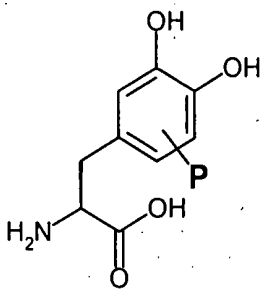


Figure 5

GABA Analog Derivatives and L-Dopa Derivatives



Generalized GABA Analog



Optionally Protected L-Dopa Analog

R14, R15, R16, R19 and R20 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl,aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl;

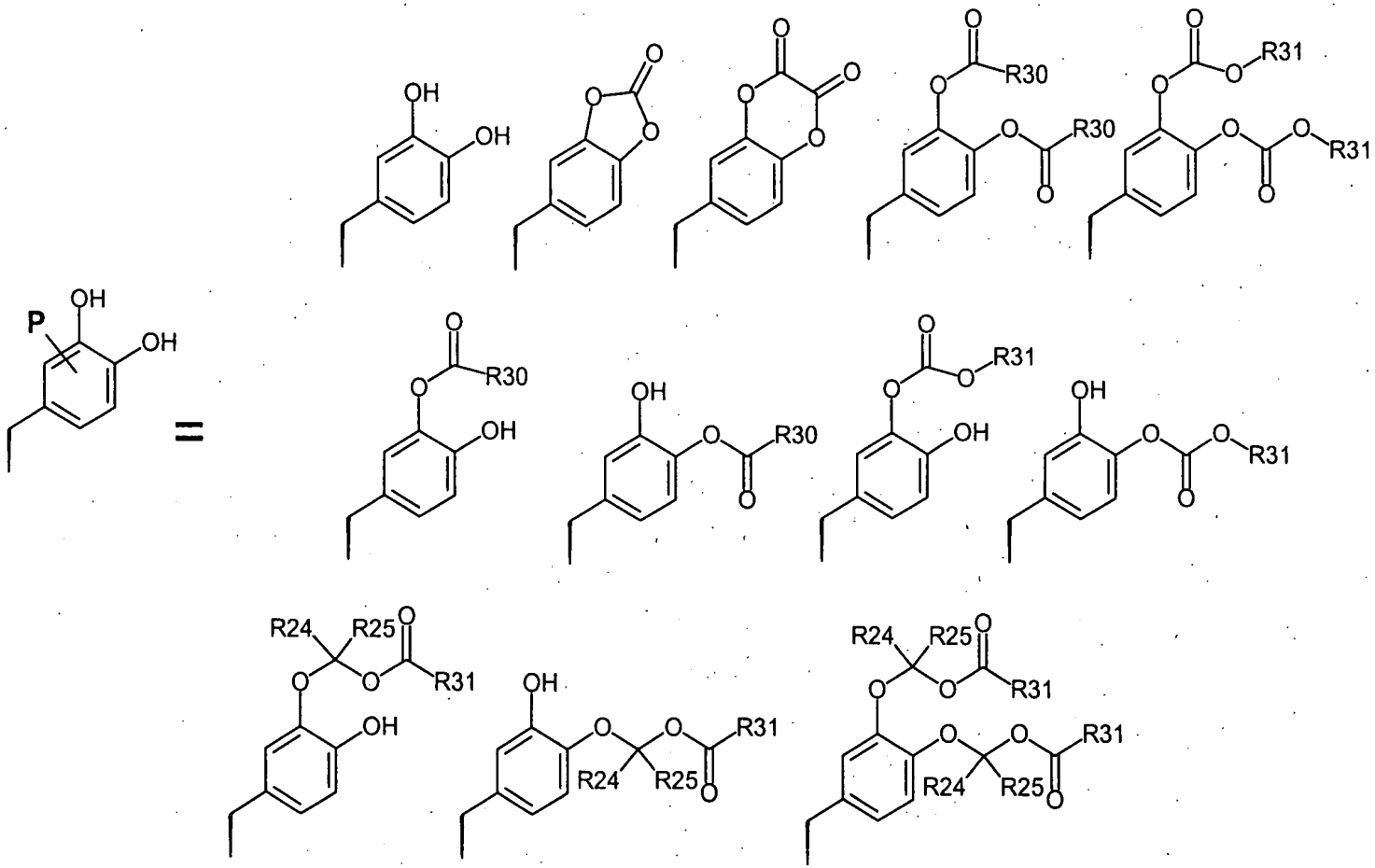
R17 and R18 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl,acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted het roaryl, heteroarylalkyl and substituted heteroarylalkyl or optionally, R17 and R18 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl or bridged cycloalkyl ring;

P is a catechol protecting group (see Figure 6)

The GABA analog or L-Dopa analog is attached to the steroid nucleus in (I-a) or (I-b) either by replacement of one of the amino hydrogen atoms, or a hydrogen atom from one of the hydroxy groups of the catechol, or the hydroxyl group of the carboxyl moiety by a covalent bond to Y^a or Y^b

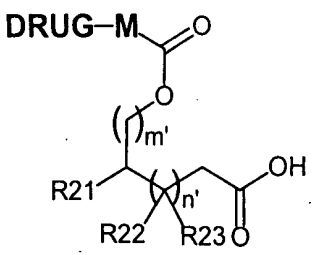
Figure 6:

Catechol Protection Strategies Applicable for L-Dopa Bile Acid Conjugates

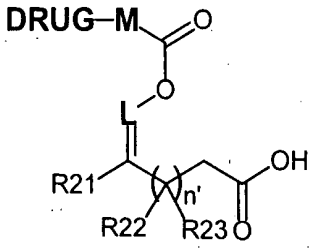


R30 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
R31 = alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
R24, R25 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
or R24 and R25 together with the carbon to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl ring

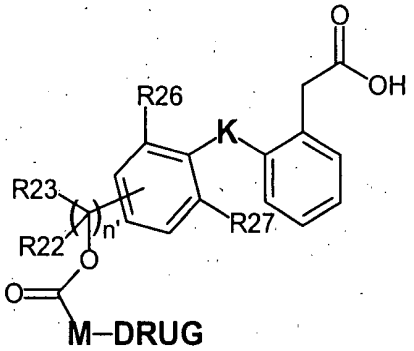
Figure 7 - Prodrugs For Enterohepatic Circulation via Intestinal and Liver Anion Transporters



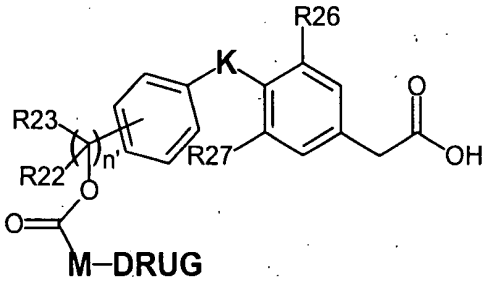
(XII)



(XIII)



(XIV)



(XV)

M = O , NR7 , CR8R9 m' is 0 to 6 ; n' is 0 to 6

L = CR8 , N

K = O , NR7 , CR8R9 ; $S(O)_j$, j = 0, 1, or 2

Each of R21 to R23 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alklysulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkylthio, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy and substituted heteroaryloxy

Preferably R22 and R23 are independently selected from the group consisting of hydrogen, alkyl and substituted alkyl

R26 and R27 are independently selected from the group consisting of halo and lower alkyl (including branched alkyl)

Figure 8

Enterohepatic Circulation Mediated by Intestinal Peptide and Hepatic Anion Transporters

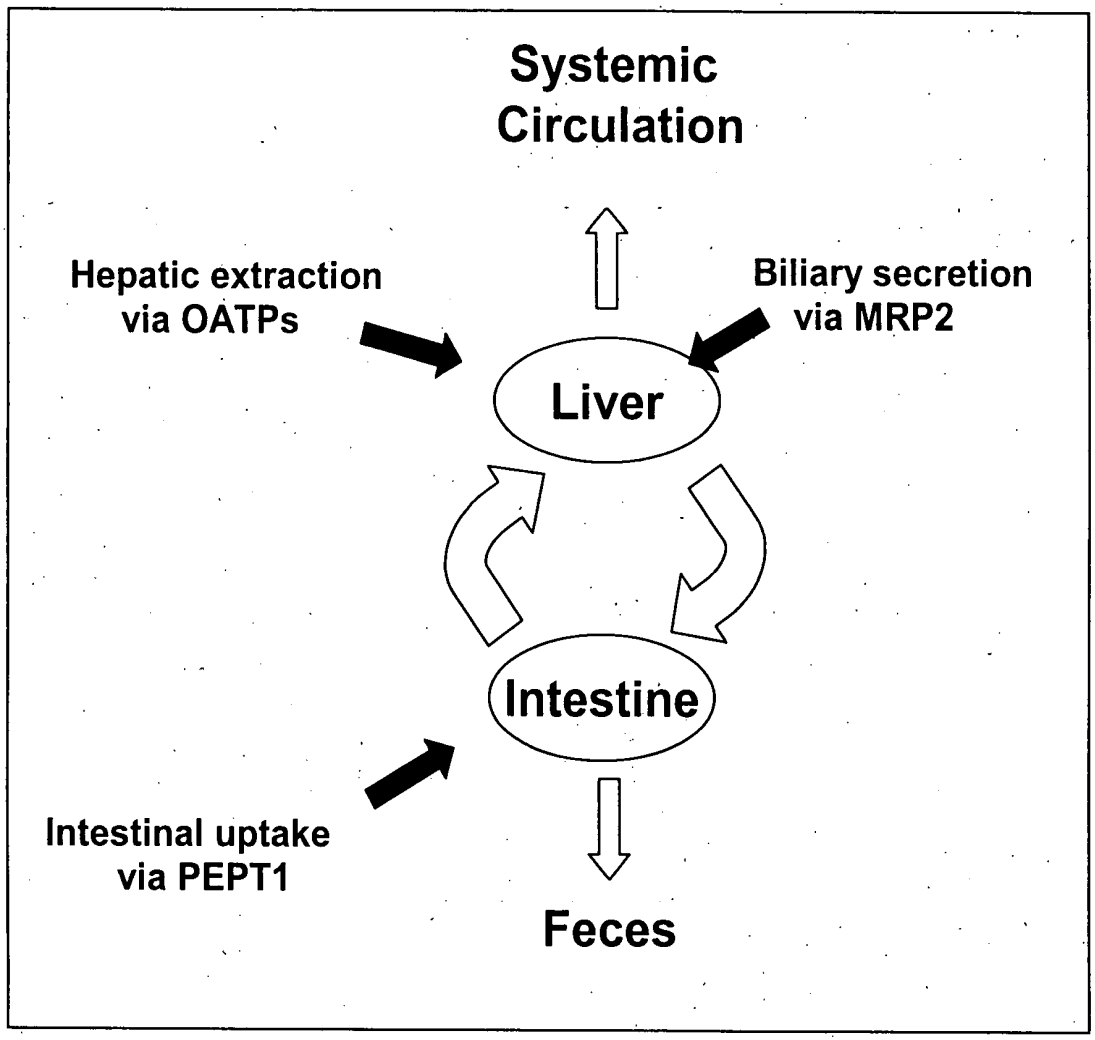
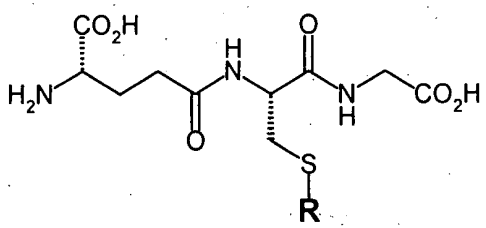


Figure 9

Enterohepatic Recirculating Prodrugs Based On Glutathione Mimetics

Glutathione Conjugate

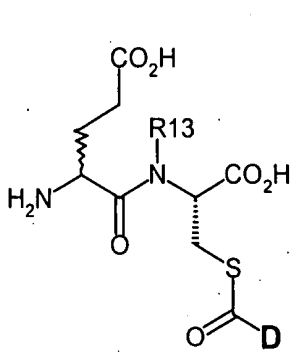


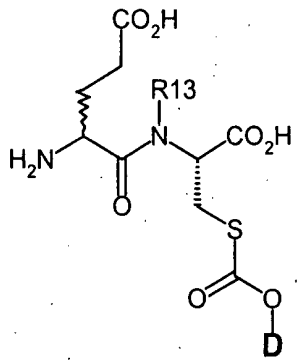
Substrate for OATP on sinusoidal membrane of liver

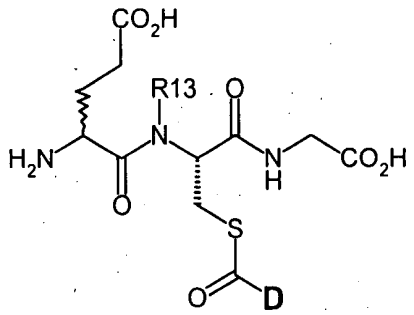
Subtrate for MPR2 on canilicular membrane of liver

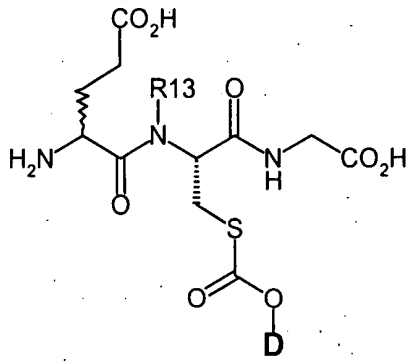
Not transported by PEPT1

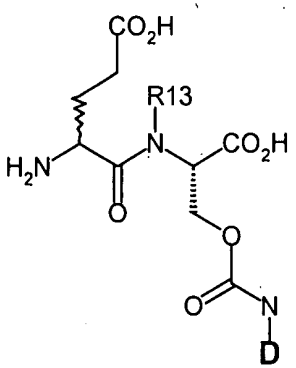
Examples of Di- and Tripeptide Prodrugs of Hydroxyl, Amine and Carboxylic Acid-Containing Drugs Based on Glutathione-Like Motif

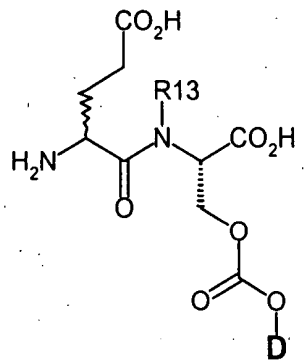


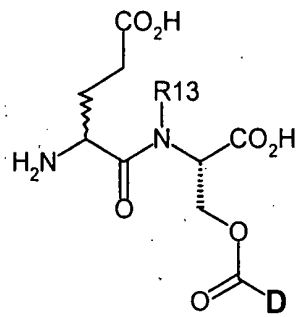


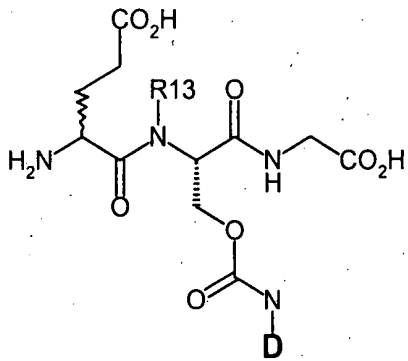


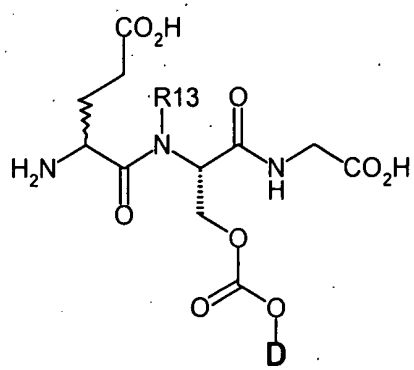












R13 = H , lower alkyl

Use PEPT1 substrate with metabolically stable di- or tripeptide backbone to achieve intestinal absorption

Figure 10

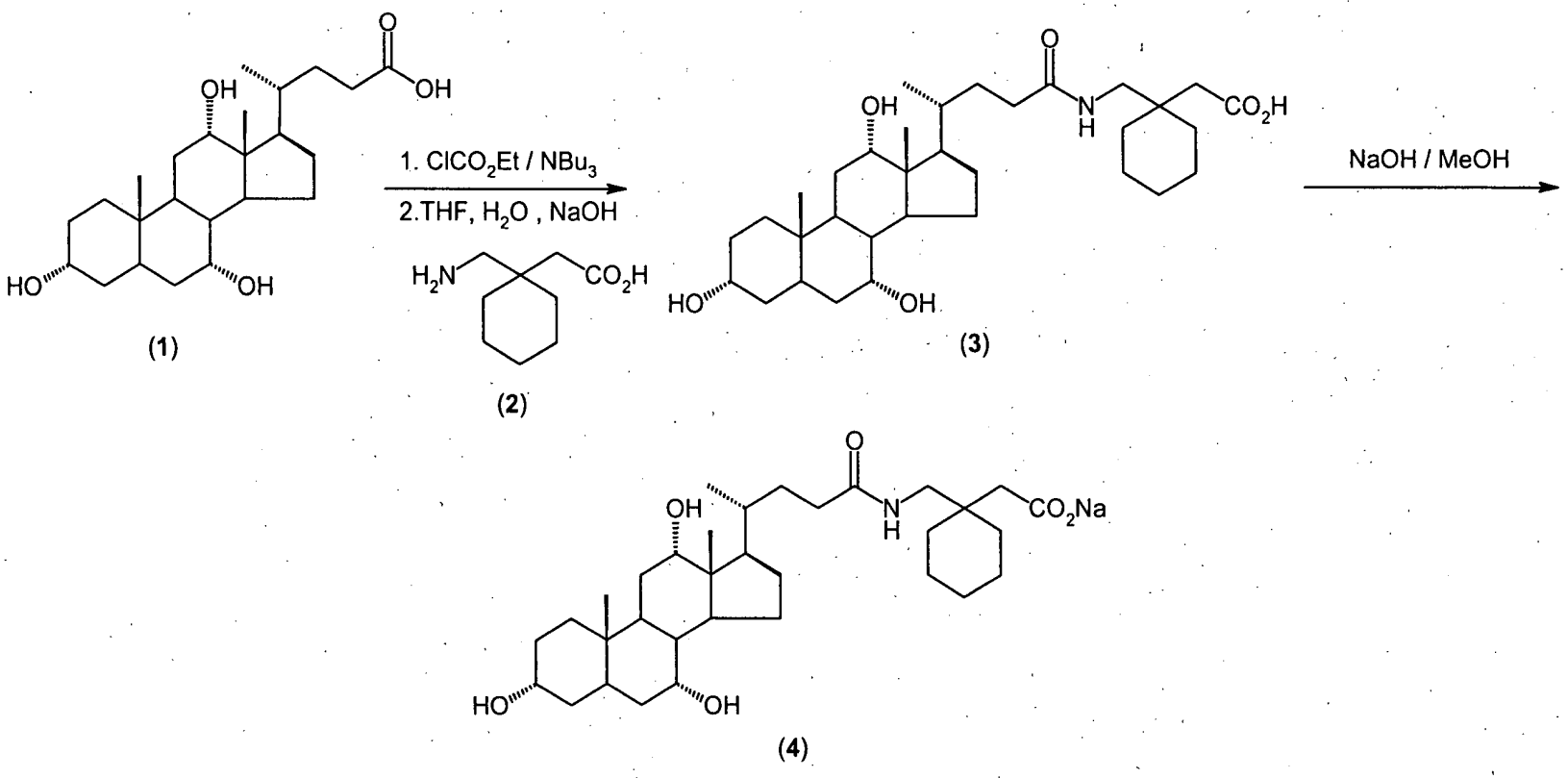
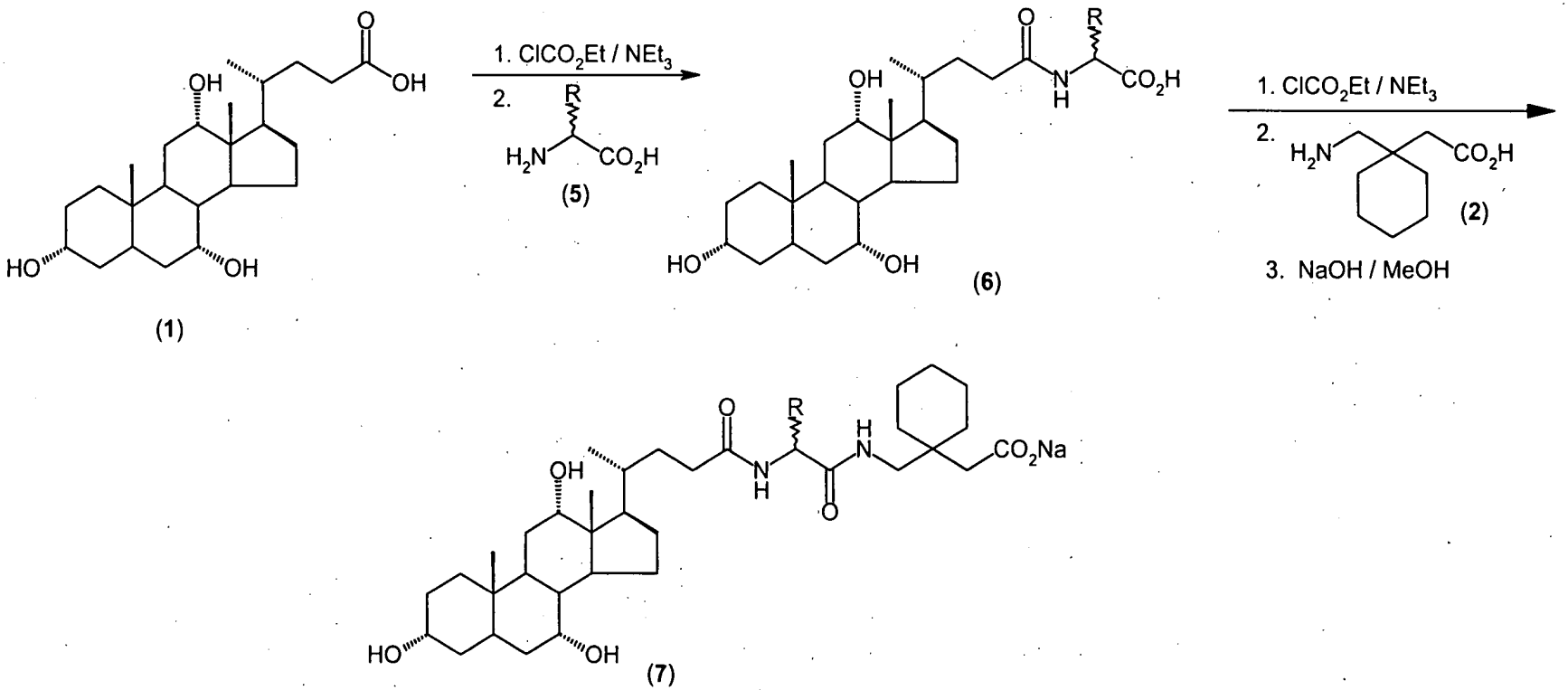
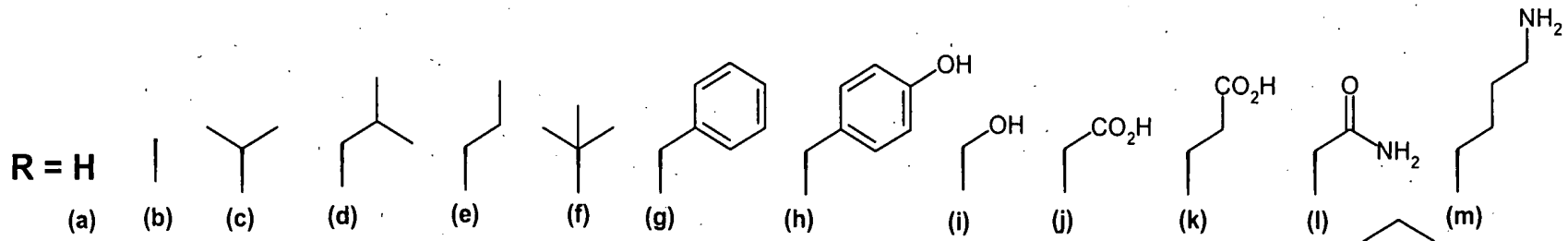
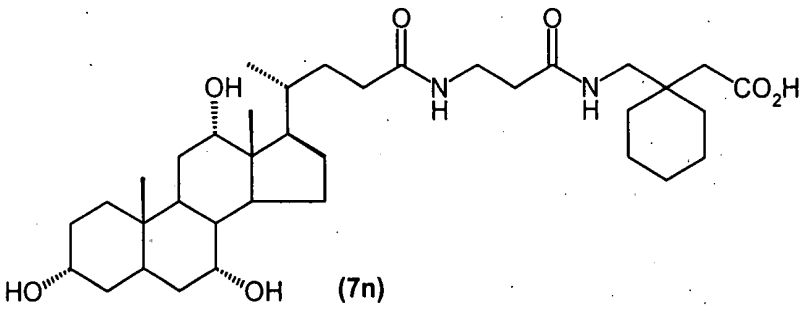


Figure 11


1. ClCO2Et / NEt3
2.
(5)
(1)
(6)
1. ClCO2Et / NEt3
2.
(2)
3. NaOH / MeOH
(7)


R = H
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
(j)
(k)
(l)
(m)


(7n)

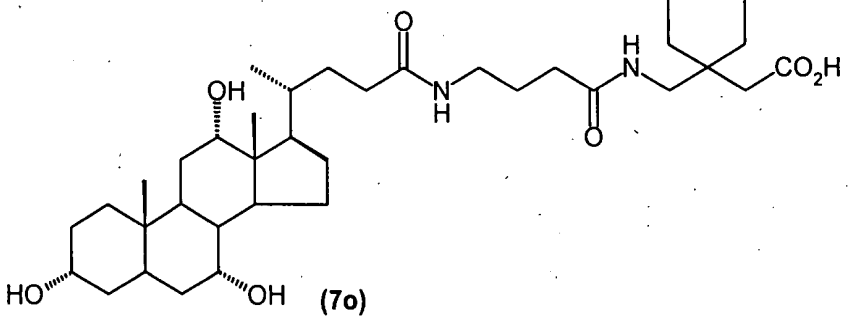

(7o)

Figure 12

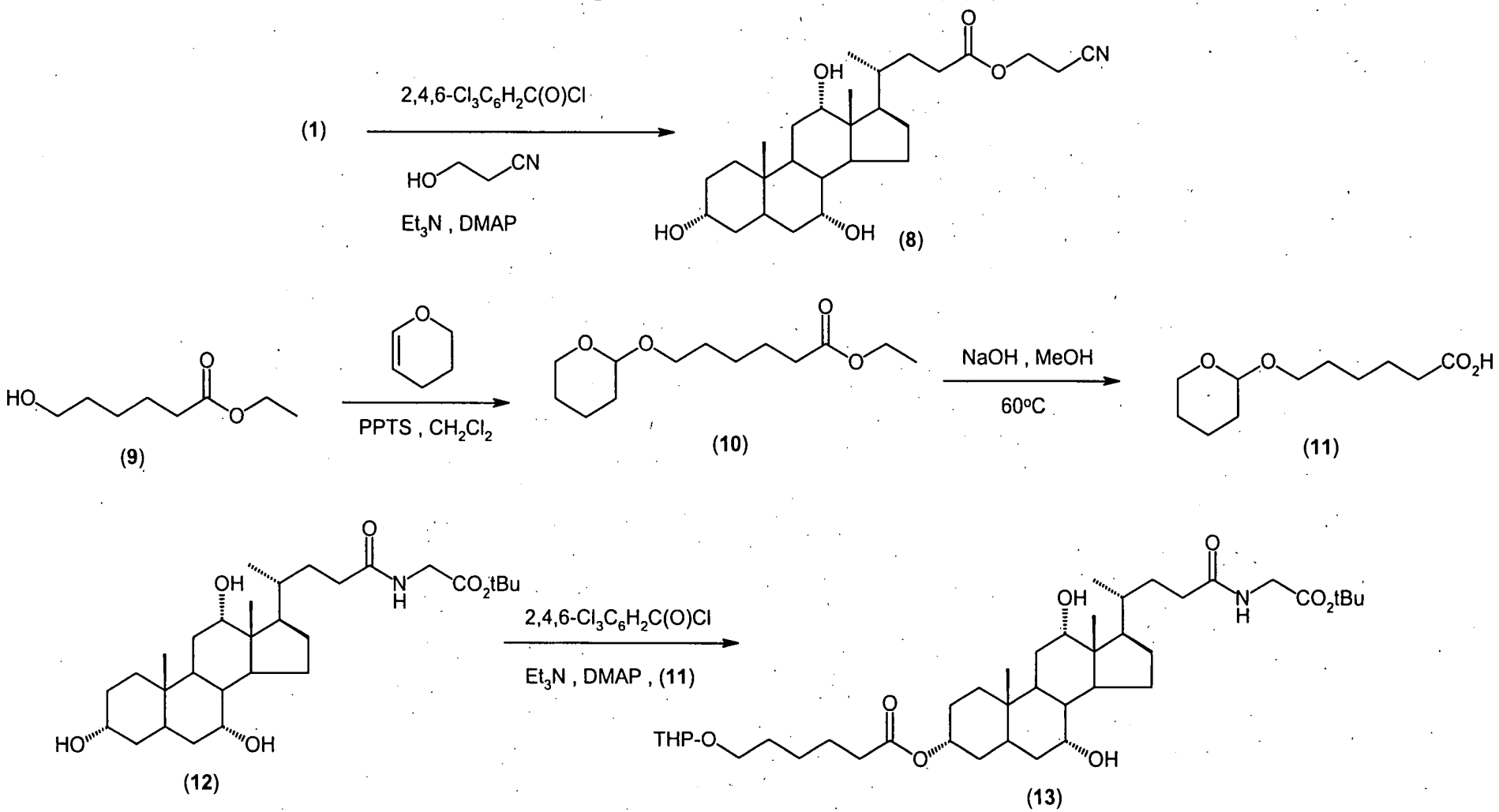

(1)
2,4,6-Cl3C6H2C(O)Cl
HO
CN
Et3N , DMAP
OH
HO
OH
O
O
CN
(8)
HO
O
O
(9)
O
PPTS , CH2Cl2
O
O
O
(10)
NaOH , MeOH
60°C
O
O
CO2H
(11)
OH
HO
OH
O
N
H
CO2tBu
(12)
2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP , (11)
THP-O
O
O
OH
OH
O
N
H
CO2tBu
(13)

Figure 13

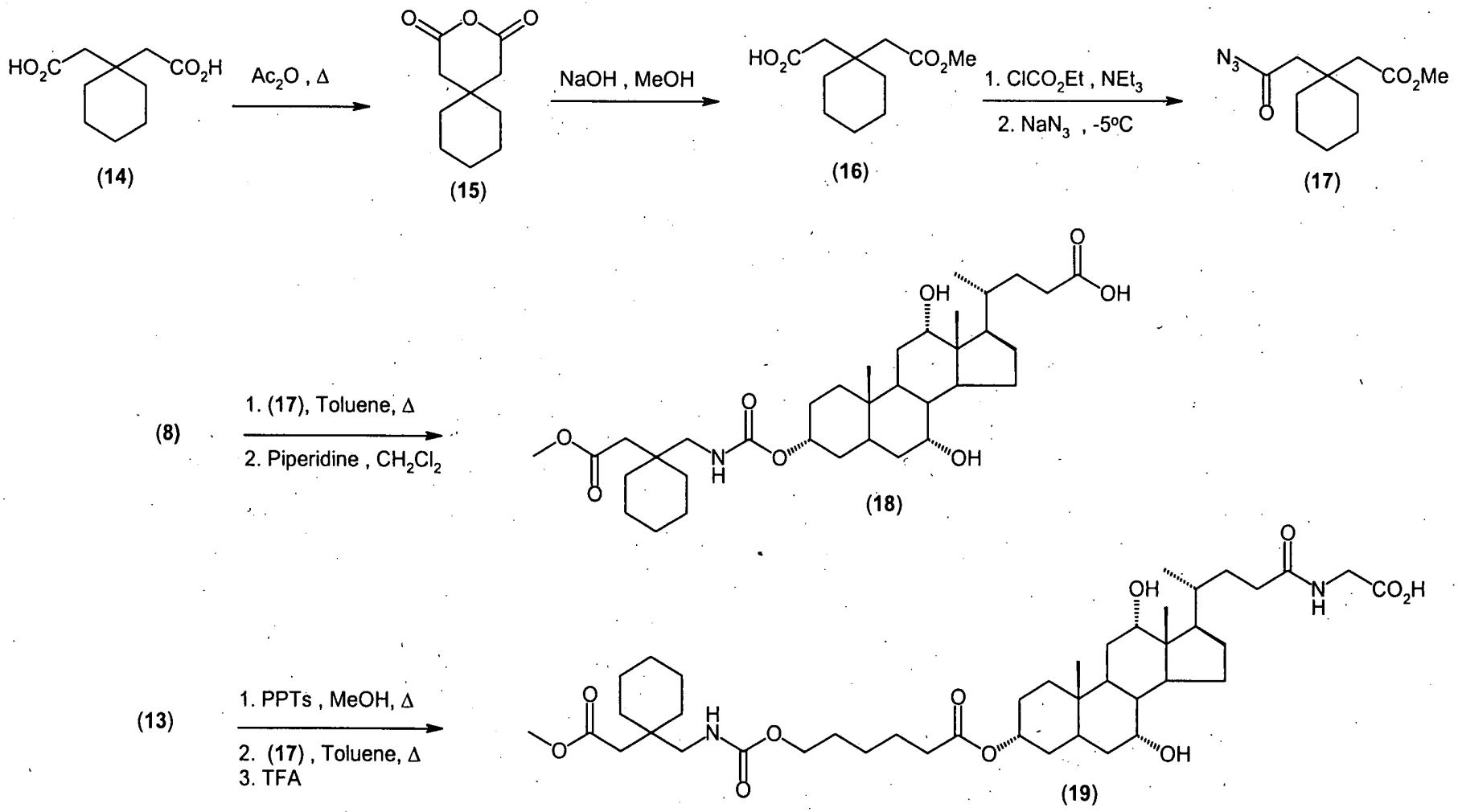

HO2C
CO2H
Ac2O , Δ
(14)
(15)
NaOH , MeOH
HO2C
CO2Me
(16)
1. ClCO2Et , NEt3
2. NaN3 , -5ºC
N3
CO2Me
(17)
(8)
1. (17), Toluene, Δ
2. Piperidine , CH2Cl2
OH
OH
OH
(18)
(13)
1. PPTs , MeOH, Δ
2. (17) , Toluene, Δ
3. TFA
OH
N
H
CO2H
(19)

Figure 14 - Synthesis of Cholyl-Dopa Conjugates

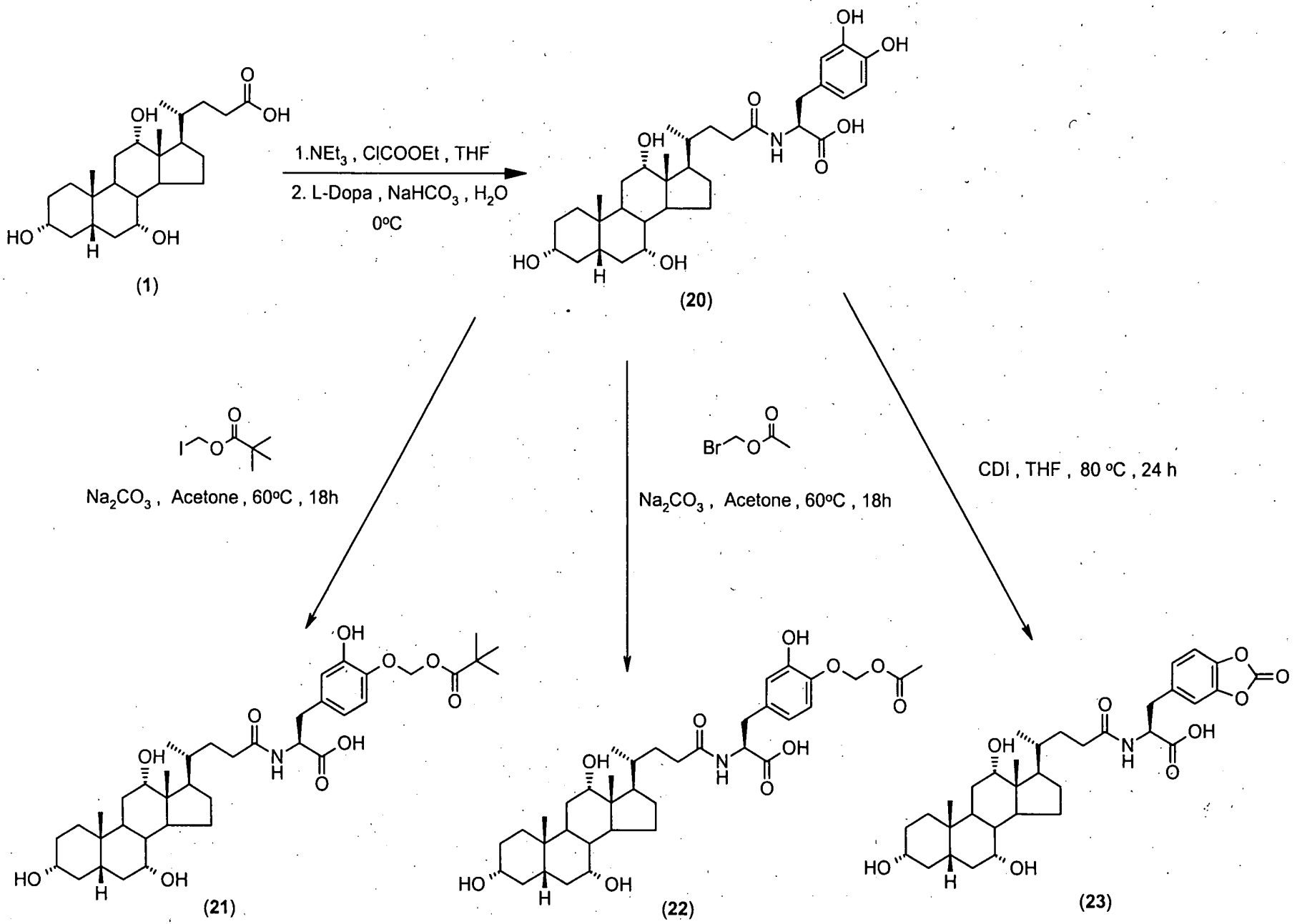


Figure 15

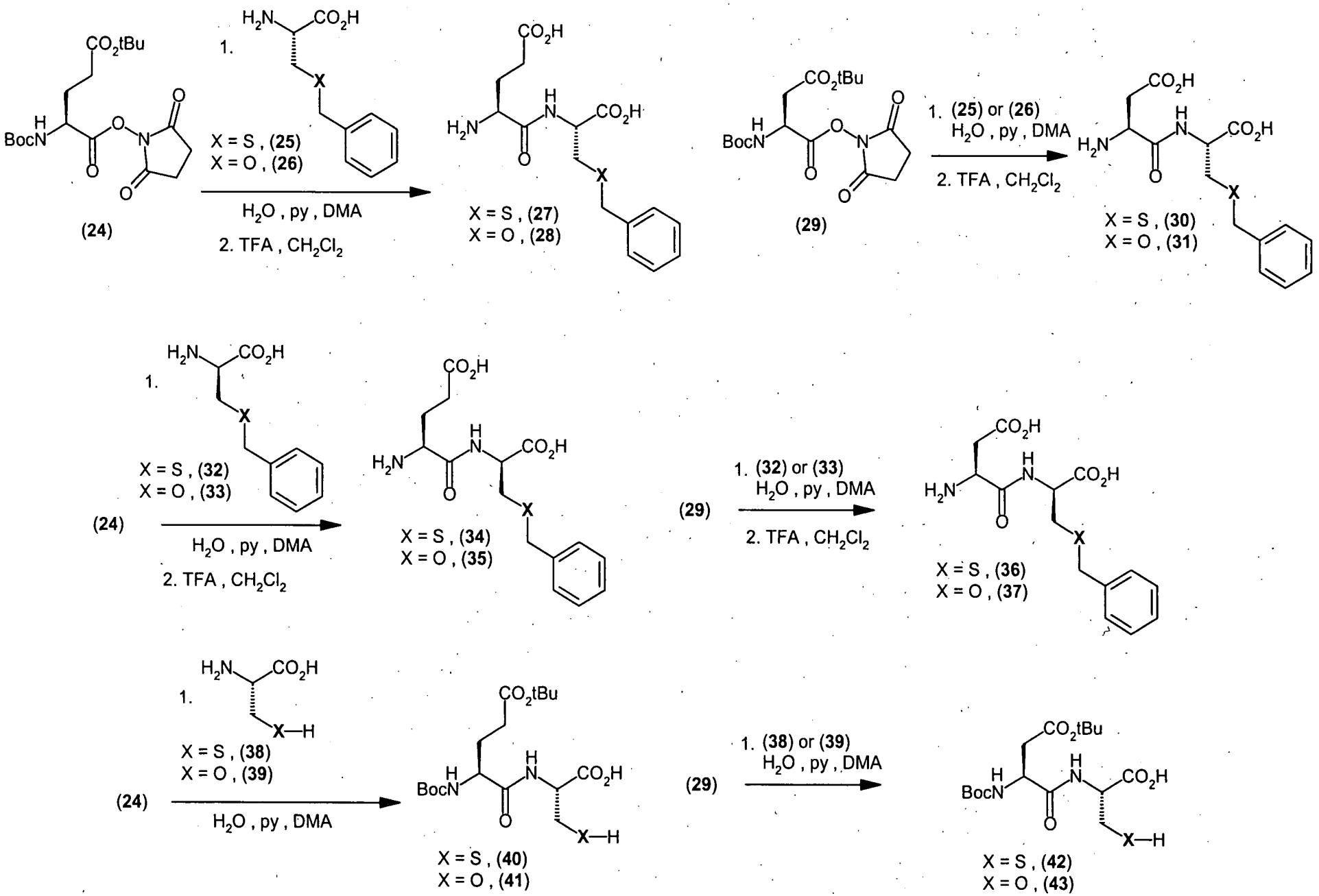

1.
X = S , (25)
X = O , (26)
H2O , py , DMA
2. TFA , CH2Cl2
(24)
X = S , (27)
X = O , (28)
(29)
1. (25) or (26)
H2O , py , DMA
2. TFA , CH2Cl2
X = S , (30)
X = O , (31)
1.
X = S , (32)
X = O , (33)
(24)
H2O , py , DMA
2. TFA , CH2Cl2
X = S , (34)
X = O , (35)
(29)
1. (32) or (33)
H2O , py , DMA
2. TFA , CH2Cl2
X = S , (36)
X = O , (37)
1.
X = S , (38)
X = O , (39)
(24)
H2O , py , DMA
X = S , (40)
X = O , (41)
(29)
1. (38) or (39)
H2O , py , DMA
X = S , (42)
X = O , (43)

Figure 16

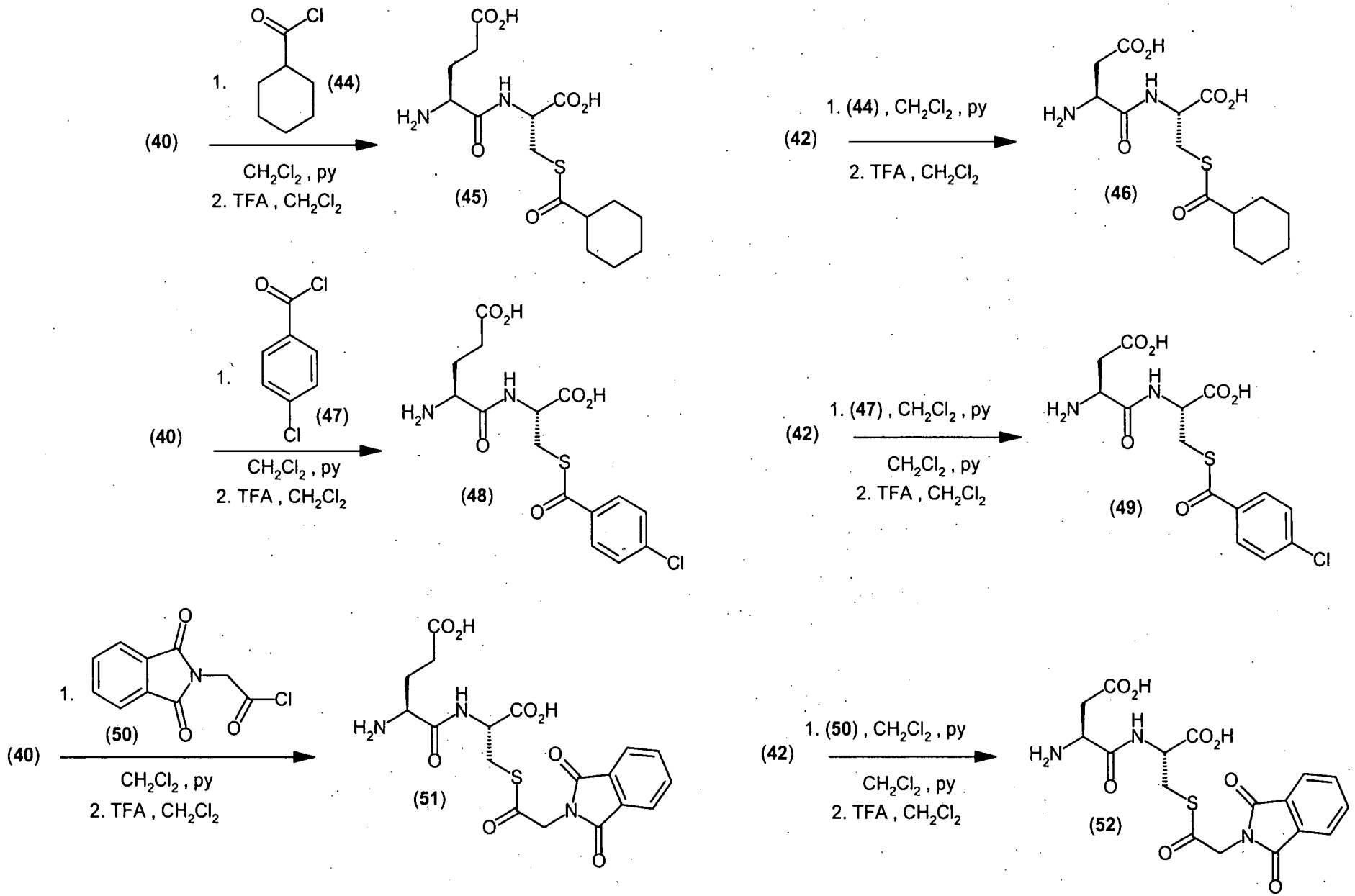
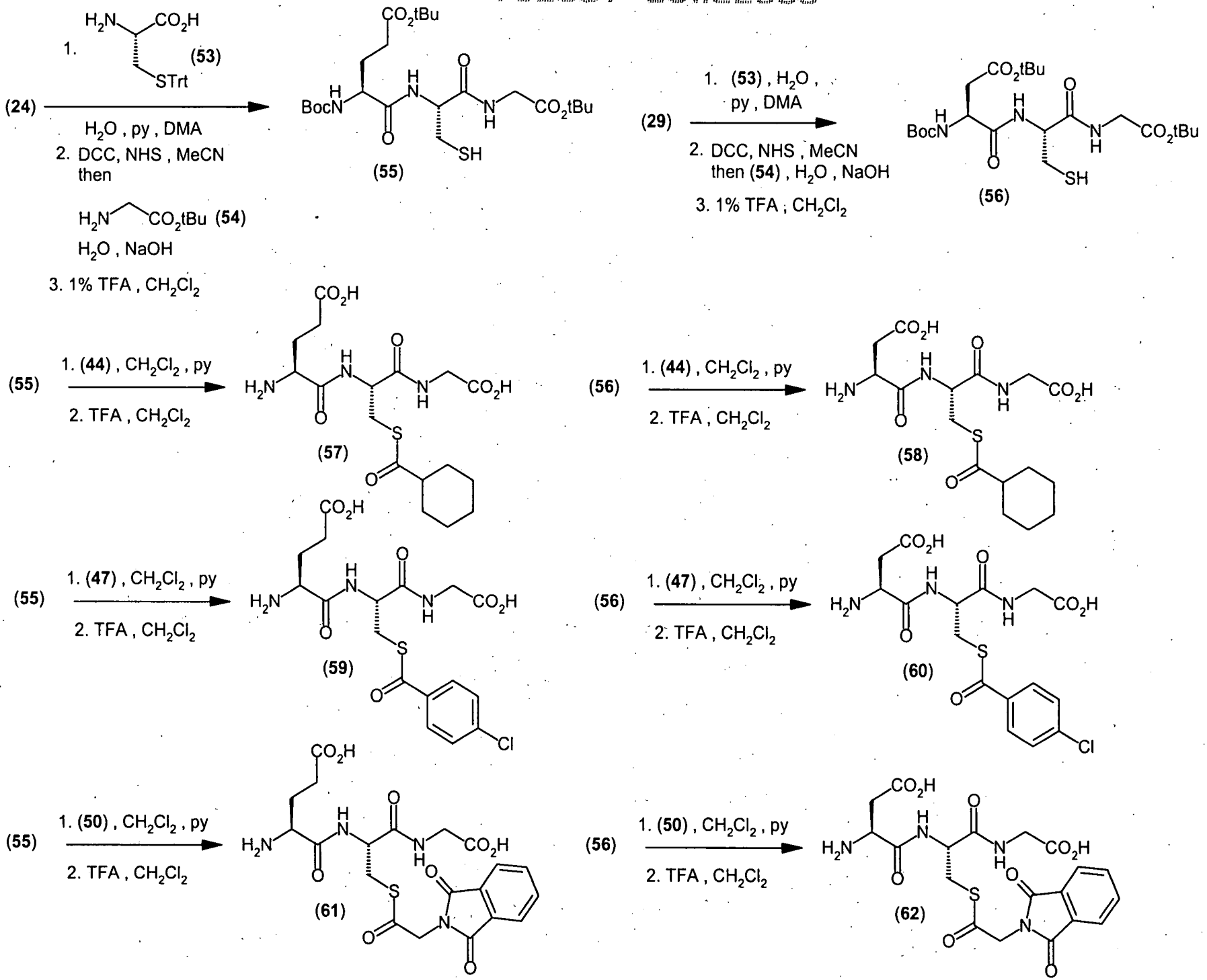

(40)
1.
(44)
CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(45)
(42)
1. (44) , CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(46)
(40)
1.
(47)
CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(48)
(42)
1. (47) , CH_2Cl_2 , py
CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(49)
(40)
1.
(50)
CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(51)
(42)
1. (50) , CH_2Cl_2 , py
CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(52)

Figure 17


1.
(53)
STrt
(24)
H2O , py , DMA
2. DCC, NHS , MeCN
then
(55)
1. (53) , H2O ,
py , DMA
(29)
2. DCC, NHS , MeCN
then (54) , H2O , NaOH
3. 1% TFA ; CH2Cl2
(56)
H2N CO2tBu (54)
H2O , NaOH
3. 1% TFA , CH2Cl2
(55)
1. (44) , CH2Cl2 , py
2. TFA , CH2Cl2
(57)
(56)
1. (44) , CH2Cl2 , py
2. TFA , CH2Cl2
(58)
(55)
1. (47) , CH2Cl2 , py
2. TFA , CH2Cl2
(59)
(56)
1. (47) , CH2Cl2 , py
2. TFA , CH2Cl2
(60)
(55)
1. (50) , CH2Cl2 , py
2. TFA , CH2Cl2
(61)
(56)
1. (50) , CH2Cl2 , py
2. TFA , CH2Cl2
(62)